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Catalytic enantioselective *syn* hydration of enones in water using a DNA-based catalyst

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The enantioselective addition of water to olefins in an aqueous environment is a common transformation in biological systems, but was beyond the ability of synthetic chemists. Here, we present the first examples of a non-enzymatic catalytic enantioselective hydration of enones, for which we used a catalyst that comprises a copper complex, based on an achiral ligand, non-covalently bound to (deoxy)ribonucleic acid, which is the only source of chirality present under the reaction conditions. The chiral β-hydroxy ketone product was obtained in up to 82% enantiomeric excess. Deuterium-labelling studies demonstrated that the reaction is diastereospecific, with only the *syn* hydration product formed. So far, this diastereospecific and enantioselective reaction had no equivalent in conventional homogeneous catalysis.

Although nature is remarkably adept at routinely using water as a nucleophile in the enantioselective synthesis of chiral molecules[1], this remains a major challenge to modern synthetic chemistry, especially in aqueous media[2–5]. An important transformation in this respect is the asymmetric conjugate addition of water to α,β-unsaturated ketones, which provides chiral β-hydroxy ketones, a key structural motif in many natural products. Hydratase enzymes, such as fumarase and enoyl-CoA hydratase, achieve this enantioselective transformation in *anti*- or *syn*-selective fashion, albeit with generally high substrate specificity[6–9]. In contrast, despite significant progress in aqueous-phase catalysis, including catalytic asymmetric synthesis[10,11], so far the enantioselective hydration of enones has eluded homogeneous catalysis. Here we present the first non-enzymatic diastereospecific and enantioselective hydration of α,β-unsaturated ketones with and in water that results in chiral β-hydroxy ketones from the *syn* addition of water, with up to 82% enantiomeric excess (e.e.).

Strategies are available for the catalytic asymmetric synthesis of the β-hydroxy carbonyl compounds, most notably the hydrogenation of β-keto esters[12], and the aldol[13,14] and oxa-Michael reactions[15]. For the oxa-Michael addition, an enantioselective formal hydration of enones was achieved by conjugate addition of an oxygen nucleophile, such as an oxime, followed by reduction to yield the β-hydroxy ketone[16]. The phosphine-catalysed conjugate addition of water to access racemic β-hydroxy carbonyl compounds has also been reported[17]. To the best of our knowledge, no examples of the enantioselective conjugate addition of water by a homogeneous catalyst are reported as yet.

The (deoxy)ribonucleic acid (DNA)-based catalytic system presented here overcomes several challenges to the enantioselective conjugate addition of water, including the intrinsic reversibility of hydration and the poor nucleophilicity of water under neutral conditions. That many chiral catalysts require anhydrous conditions to function optimally further complicates this reaction, which makes a DNA-based catalyst more attractive.

DNA-based asymmetric catalysis, a concept we introduced recently, proves to be a powerful approach to achieving asymmetric catalysis in water[18]. The DNA-based catalyst consists of a catalytically active copper(II) complex (Cu–L), which is positioned in close proximity to the DNA helix through non-covalent interactions. Salmon testes DNA (st-DNA), which is natural DNA that consists of duplex fragments approximately 2,000 base pairs long, is generally used as the DNA source. In taking this approach, the inherent chirality of DNA was employed to achieve high enantioselectivities in several key C–C bond-forming reactions, such as the copper-catalysed Diels–Alder, Michael addition and Friedel–Crafts alkylation reactions[19–21]. Enantioselective fluorinations and allylic aminations using DNA-based catalysts have also been reported[22,23]. In our studies of the transformations of enones catalysed by Cu–L/st-DNA, we discovered, serendipitously, the first examples of enantioselective conjugate addition of water in water that result in the enantiomerically enriched β-hydroxy ketone product.

Results and discussion

The model reaction in the present study is the hydration of α,β-unsaturated 2-acyl imidazole **1a** to give the β-hydroxy ketone **2a** (Fig. 1). Using the Cu^{2+} complex of 4,4′-dimethyl-2,2′-bipyridine (Cu–**L1**) and st-DNA (the DNA-based catalyst that provided the highest enantioselectivities in all C–C bond-forming reactions reported to date), **2a** was obtained with a modest 19% e.e. In contrast, the highest enantioselectivities were obtained with the first generation of ligands[18], which comprise a 9-aminoacridine intercalating moiety connected to an aminomethylpyridine metal-binding domain by a spacer (Fig. 1). The best results were obtained using **L2**, with 55% conversion and 72% e.e. after 24 hours for the *R*-enantiomer of **2a** (Table 1, entry 2). Generally, lower conversions and enantioselectivities were obtained with the related ligands **L3**–**L5** (Table 1, entries 3–5). The absolute configuration of the hydration product was established by converting **2a** into the corresponding β-hydroxy carboxylic ester, described previously (see Supplementary Information)[24]. This corresponds to the attack of water from the *re*-face of the enone. A series of control experiments confirmed that the enantioselectivity was induced by hydration of the alkene and was not the result of an enantioselective retro-aldol/aldol reaction (see Supplementary Information).

The catalyst concentration could be lowered to 3 mol% in copper (ratio of base pairs DNA:Cu–**L2**, 6:1) with only a small decrease in the enantiomeric excess (Table 1, entry 6), albeit the conversion did

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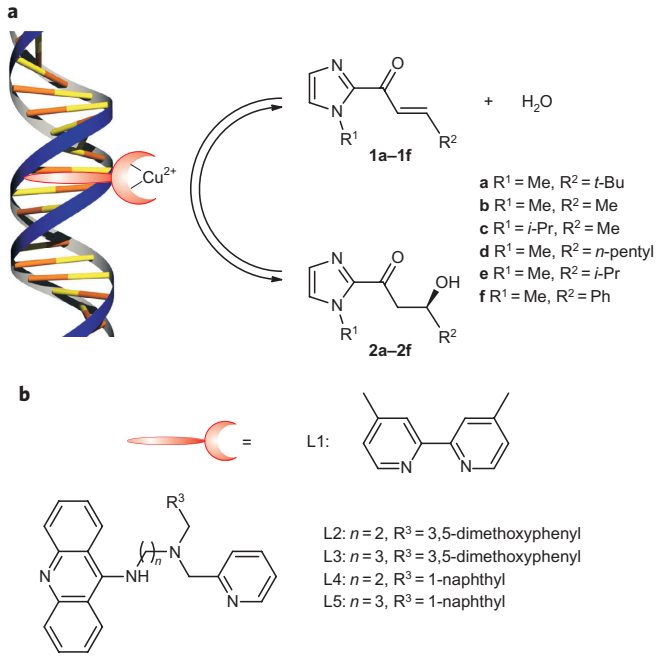

Figure 1 | Enantioselective hydration of α,β-unsaturated ketones. **a**, Schematic representation of the DNA-based catalyst and general reaction scheme of the catalytic enantioselective hydration of a variety of α,β-unsaturated 2-acyl-(1-alkyl)imidazole substrates. **b**, Overview of ligands used in this study: ligand **L1** is 4,4′-dimethyl-2,2′-bipyridine and **L2**–**L5** are based on 2-(aminomethyl)pyridine.

not reach the same level, even after prolonged reaction. When the reaction was performed in the absence of ligand, but in the presence of st-DNA and $Cu(NO_3)_2$, the *S*-enantiomer of **2a** was obtained with 42% e.e. (Table 1, entry 7). This is the opposite enantiomer compared with that obtained in the presence of a ligand (Table 1, entries 1–6). In the absence of Cu^{2+}, conversion was not observed. Taken together, this demonstrated that Cu^{2+} was necessary for the activation of the enone in the hydration step, that the catalytic species was the ligand-bound copper ion and that the combination of ligand and DNA dictated the stereochemical outcome of the reaction. Based on these preliminary results, Cu–**L2**/st-DNA was selected for further study.

The substrate scope of the enantioselective hydration reaction was investigated (Table 1, entries 8–12). In all cases with R^2 as the alkyl group, the reaction proceeded cleanly to give the hydrated product. It was found that both the enantiomeric excess and the maximum conversion obtained were dependent on the steric bulk of R^2. Full conversion was achieved for $R^2 = CH_3$, whereas for R^2 = isopropyl or *n*-pentyl the maximum conversion was 90%. The enantiomeric excess was determined before the maximum conversion was reached, because this generally provided higher enantiomeric excess (see below). A clear relation between enantiomeric excess (from 28 to 72% e.e.) and the steric bulk of R^2 was observed: the enantiomeric excess followed the order methyl < *n*-pentyl < *i*-propyl < *t*-butyl. Substitution of R^1 by an isopropyl group led to the complete loss of enantioselectivity (Table 1, entry 9). With R^2 = phenyl, conversion was not observed (Table 1, entry 12), which can be attributed to the thermodynamically unfavourable hydration of such a highly conjugated substrate (see below).

The reaction was scaled up to 0.10 mmol **1a** (17 mg) to give **2a** in 48% isolated yield and 66% e.e. After extraction with diethyl ether, the aqueous fraction that contained the catalyst could be recycled four times by adding **1a** again, with no loss in conversion or enantiomeric excess.

The hydration of **1a** catalysed by Cu–**L2**/st-DNA was monitored by high-performance liquid chromatography (HPLC). It was found that the optimal reaction time, with respect to both conversion and enantiomeric excess, was 24 hours. After this period the conversion increased further to 65%, albeit at a cost to the enantiomeric excess, which decreased significantly until a final value of 23% for the *S*-enantiomer, the opposite enantiomer to that formed initially in the reaction (Fig. 2a).

These observations can be explained by considering the reversible nature of hydration reactions; the reaction reached its equilibrium composition at 65% conversion of **1a**, which corresponds to a K_{eq} of 1.9 ([**2a**]/[**1a**]). The reversibility of the reaction also explains the observed decrease in enantioselectivity over prolonged reaction times. In the initial stages of the reaction *R*-**2a** was formed preferentially. Microscopic reversibility dictated that for the reverse reaction from **2a** to **1a** the *R*-enantiomer was converted preferentially also, which resulted in a decrease in the enantioselectivity once the dehydration became significant. Indeed, from pure racemic **2a**, 35% conversion into **1a** and a final 23% e.e. for the *S*-enantiomer of the remaining **2a** was found, which demonstrated that the *R*-enantiomer was dehydrated preferentially (Fig. 2b). In the pre-equilibrium stage this process is a kinetic resolution for which a selectivity factor of $S = 4.0$ was calculated. A similar equilibrium composition and enantiomeric excess was obtained from pure enantioenriched *R*-**2a**.

Taken together, in the catalytic hydration of **1a** the kinetic product *R*-**2a** formed first. Then *R*-**2a** slowly racemized because of the kinetic resolution back to **1a**, and eventually the *S*-enantiomer of **2a** remained at 23% e.e. The *S*-enantiomer was obtained in excess under equilibrium conditions, so a difference in free energy

Table 1 | Reaction optimization and substrate scope.

Entry	Starting material	Product	Ligand	Reaction time (h)	Conversion* (%)	e.e.† (%)
1	**1a**	**2a**	**L1**	24	14	19 (*R*)
2	**1a**	**2a**	**L2**	24	55	72 (*R*)
3	**1a**	**2a**	**L3**	24	20	24 (*R*)
4	**1a**	**2a**	**L4**	24	36	55 (*R*)
5	**1a**	**2a**	**L5**	24	24	20 (*R*)
6‡	**1a**	**2a**	**L2**	72	33	62 (*R*)
7	**1a**	**2a**	-	24	20	42 (*S*)
8	**1b**	**2b**	**L2**	7	100	28
9	**1c**	**2c**	**L2**	7	100	3
10	**1d**	**2d**	**L2**	7	75	47
11	**1e**	**2e**	**L2**	7	71	60
12	**1f**	**2f**	**L2**	24	0	n.d.

Standard conditions: 5 °C, 20 mM MES buffer, pH 5.5, 15 μmol **1** (1 mM), 1.3 mg ml^{-1} st-DNA (2 mM base pairs), 0.39 mM ligand, 0.3 mM $Cu(NO_3)_2$, unless noted otherwise. *Determined by ^{1}H NMR spectroscopy. †Determined by HPLC using a chiral stationary phase. ‡0.14 mg ml^{-1} st-DNA, 0.039 mM ligand, 0.03 mM $Cu(NO_3)_2$. n.d. = not determined.

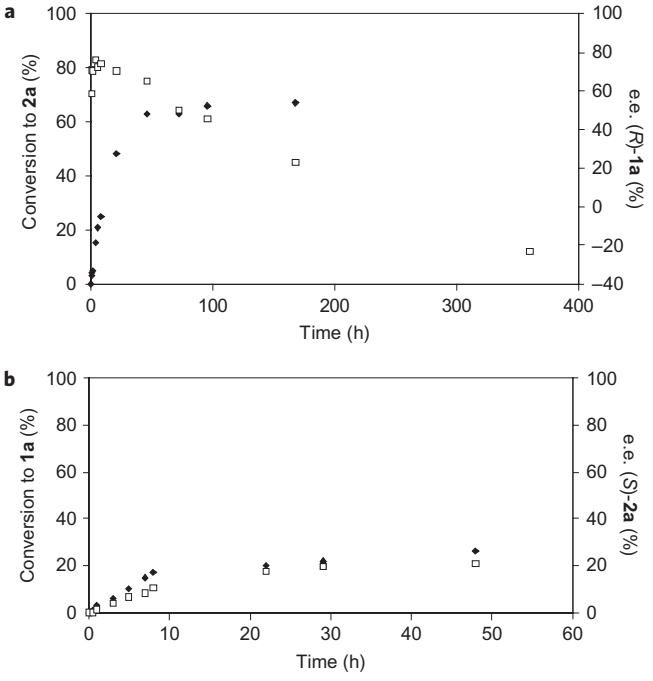

Figure 2 | Temporal evolution of enantiomeric excess and conversion. **a**, The hydration of **1a** into **2a** over time. The enantiomeric excess (of *R*-**2a**) is depicted as open squares and the conversion of **1a** into **2a** as closed diamonds. **b**, The dehydration of **2a** into **1a** over time. The enantiomeric excess of the remaining substrate (*S*-**2a**) is depicted as open squares and the conversion of **2a** into **1a** as closed diamonds. Figure 2a shows the enantiomeric excess in the *R*-enantiomer, whereas Fig. 2b shows the enantiomeric excess in the *S*-enantiomer.

was induced between *R*-**2a** and *S*-**2a**. Tentatively, this could result from the formation of diastereomeric complexes with Cu–**L2**/DNA.

The stereochemical course of the hydration reaction was elucidated further by carrying out the transformation with D_2O as solvent. The reaction in D_2O was slower than that in H_2O, but the equilibrium shifted towards the product: after three days 40% conversion and 79% e.e. was found and after seven days the conversion increased to 90% and **3a** was obtained with 73% e.e. (Fig. 3). The presence of an equilibrium isotope effect explains the higher conversion and enantioselectivity found in D_2O; apparently, **3a** is more stable than **2a**, and hence the contribution of the dehydration reaction relative to the hydration pathway is smaller.

The ^{1}H NMR spectrum of **3a** in $CDCl_3$ shows that it contains one deuterium at the α-carbon (Fig. 3). This further supports a hydration mechanism, because a retro-aldol/aldol mechanism would give rise to complete deuteration at the α-position.

The appearance of the signal for the α-protons of **2a** is the result of two different vicinal couplings of the diastereotopic protons. The rotation around the C2–C3 bond is restricted in β-hydroxy ketones because of the formation of an intramolecular hydrogen bond between the β-alcohol and the keto moiety, which is supported by infrared spectroscopy and concentration-dependent ^{1}H NMR spectroscopy (Supplementary Figs S8,S9). This results in a chair-like conformation, in which the bulky *t*-butyl moiety can be assumed to occupy the equatorial position[25]. The geminal coupling constant between the two α-protons is 15.7 Hz. The two vicinal coupling constants of 9.4 and 2.3 Hz between the α-protons and the β-proton involve the *anti* and the *gauche* protons, respectively.

The reaction of **1a** with D_2O yielded monodeuterated **3a** as a single diastereoisomer, with a vicinal coupling constant of 2.0 Hz, which indicates that the two vicinal protons are positioned in a

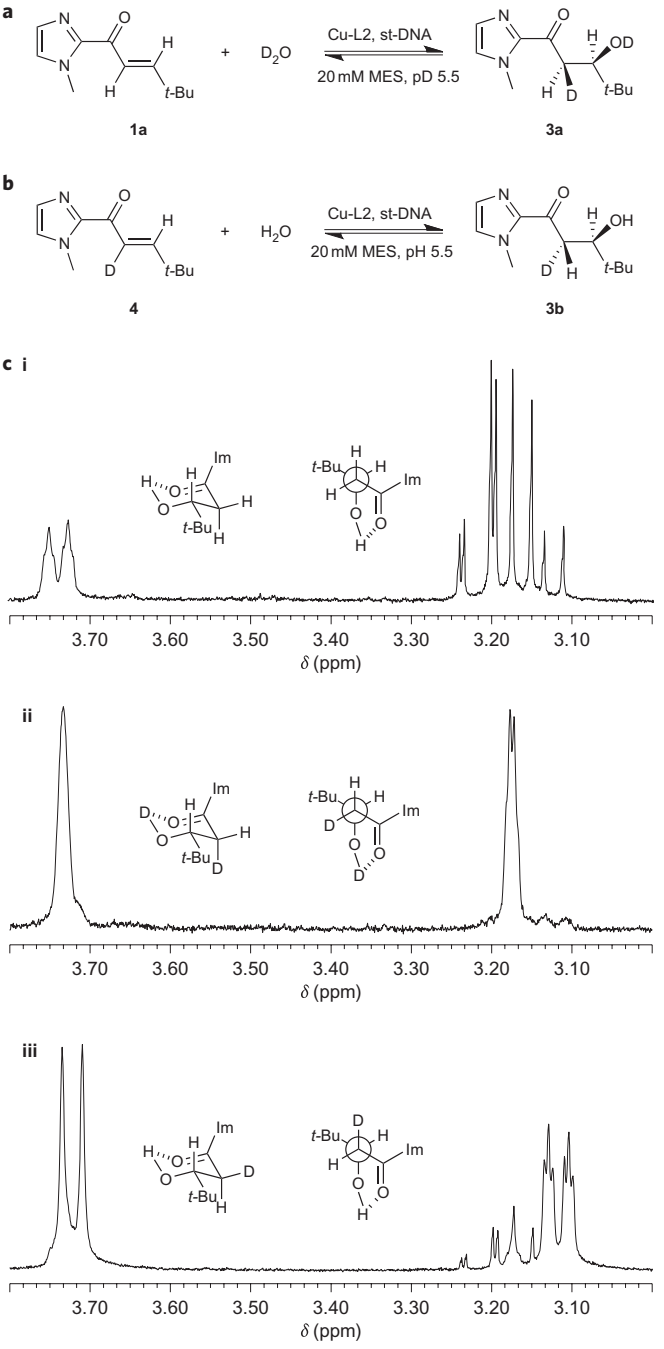

Figure 3 | Diastereospecificity of the catalytic hydration reaction. **a**, Synthesis of **3a** by hydration using D_2O and catalysed by Cu–**L2**/st-DNA. **b**, Synthesis of **3b** by hydration of deuterated substrate **4** (85% D) catalysed by Cu–**L2**/st-DNA. **c**, ^{1}H NMR spectra of **2a** (**i**), **3a** (**ii**) and **3b** (**iii**) in $CDCl_3$ in the region 3.8–3.0 parts per million (ppm), and chair conformations and Newman projections used for the conformational analysis. Signals in the 3.2–3.0 ppm region arise from the α-protons, and signals at 3.7–3.8 ppm from the β-protons. In the spectrum of **2a** (**i**), the geminal coupling constant between the two α-protons is 15.7 Hz. The two vicinal coupling constants of 9.4 and 2.3 Hz between the α-protons and the β-proton involve the *anti* and the *gauche* protons, respectively. The spectrum of **3a** (**ii**) shows a single diastereomer with a vicinal coupling constant of 2.0 Hz, which demonstrates that D_2O was added in a *syn* fashion. For the complementary experiment that gave rise to **3b**, spectrum (**iii**) shows a large vicinal coupling constant of 10.0 Hz, which corresponds to the anti-orientation between the α- and β-protons. Im = 2-(1-methyl)imidazolyl.

gauche orientation. The complementary experiment, that is the addition of water to α,β-unsaturated 2-acyl(1-methyl)imidazole **4**, which was 85% deuterium-labelled at the α-carbon, gave rise to a vicinal coupling constant of 10.0 Hz in the NMR spectrum of the β-hydroxy ketone product **3b**, which corresponds to the *anti* orientation between the α- and β-protons. These experiments prove unequivocally that the hydration of **1a** proceeds in a diastereospecific fashion. Although the assignment of the stereostructure from vicinal coupling constants is highly dependent on the substituents[25], in the present case the absence of bulky substituents on the α-position led us to conclude that the most stable conformers are shown here. Hence, from the conformational analysis it can be concluded that the hydration of **1a** catalysed by Cu–**L2**/st-DNA occurs in a *syn* fashion. Interestingly, it was observed that reaction with only $Cu(NO_3)_2$ in D_2O (that is, in the absence of DNA or ligand) also furnishes **3a** as the product. Hence, the *syn* addition of water does not result from the presence of DNA.

The enantioselectivity of the asymmetric hydration catalysed by DNA/Cu–**L2** is dependent on the DNA sequence. Evaluation of a broad range of self-complementary oligonucleotides in both H_2O and D_2O and stopping the reactions at low conversion to obtain the optimum enantiomeric excess showed that sequences with central AT base pairs gave the best results (Supplementary Table S2). The highest enantiomeric excesses were obtained with $d(CAAAAATTTTTG)_2$ and $d(GCGCTATAGCGC)_2$ in D_2O (82% e.e.). These results are in contrast with those of the Diels–Alder reactions in which the same catalyst preferred GC-rich sequences[26].

The present catalytic system is unprecedented in its ability to effect enantioselective and diastereospecific hydration of α,β-unsaturated ketones. An analysis of this catalytic system revealed that the three individual components (DNA, Cu^{2+} ion and ligand) have specific functions that are synergistic. The DNA is the only source of chirality present in the reaction and, hence, is responsible for the observed chiral induction; in the absence of DNA, no enantioselectivity was found.

The Cu^{2+} ion was required for catalysis; in the absence of copper salt no conversion was obtained. $Cu(NO_3)_2$ in combination with st-DNA gave rise to significant enantioselectivity (that is, 42% e.e.) in the catalysed hydration reaction. However, it is the ligand that modulates and fine tunes the interactions with DNA, and results in a higher reactivity and enantiomeric excess. The catalysed hydration reaction is ligand-accelerated; after three hours, a $36 \pm 3\%$ conversion of **1a** was obtained with Cu–**L2**/st-DNA compared to $16 \pm 1\%$ with $Cu(NO_3)_2$/st-DNA. Furthermore, the enantiomeric excess increased to a maximum of 72% in H_2O and 82% in D_2O. With Cu–**L2**/st-DNA the opposite enantiomer, the *R* hydration product, was obtained in excess rather than the *S*-enantiomer obtained with $Cu(NO_3)_2$/st-DNA. This result underlines the important role the ligand plays in combination with DNA in directing the stereochemical course of the reaction.

Particularly intriguing is the observed *syn* diastereospecificity, which until now was reported only for hydratase enzymes, such as enoyl-CoA hydratase. For enoyl-CoA hydratase the hydrogen atom and the hydroxyl group were from the same water molecule and *syn* diastereoselectivity was proposed to result from either a concerted or a stepwise mechanism, in which the water nucleophile was bound and directed for attack by two active-site glutamate residues[27]. In the present case, it was found that with $Cu(NO_3)_2$ alone complete *syn* diastereoselectivity was obtained as well. Apparently, neither the DNA scaffold nor the ligand are required. Therefore, it appears that the Cu^{2+} centre is responsible for the observed *syn* diastereospecificity, and ensures that both the hydroxyl group and the proton are added to the same π-face of the enone.

The hydration product that results from the approach of a water nucleophile through the *re*-face of the enone moiety is formed preferentially. By contrast, in the Diels–Alder reaction catalysed by the same catalytic system, the approach of the diene through the *si*-face is favoured[18,26]. It is highly unlikely that the coordination chemistry of the α,β-unsaturated 2-acyl imidazole and the Cu^{2+} complex is different for the hydration reaction, so selective shielding of one π-face of the enone by the DNA can be excluded as a reason for the observed enantioselectivity. Hence, different factors should be considered. The induction of enantioselectivity in the hydration reaction by the DNA might be related to the hydrogen-bonding capabilities of the nucleobases in the groove; a spine of hydration is formed in the groove, with highly localized water molecules[28]. This manifests itself, for example, when drug molecules bind to DNA, where water can be situated between the drug and the DNA[29]. Possibly, this complex fluid network also plays a role between the Cu^{2+}-bound **1a** and the DNA, in that it is involved in assisting and directing the approach of the water nucleophile, which could be either one of the groove-bound water molecules or water from the bulk solution.

In conclusion, we present the first example of non-enzymatic enantioselective and diastereospecific *syn* hydration of α,β-unsaturated ketones. The enantioselectivity clearly originates from the DNA, but the *syn* diastereospecificity was found with copper(II) salts alone, in the absence of DNA. This hydration reaction, which has no equivalent in conventional chiral transition-metal catalysis, clearly underlines the versatility of the DNA-based catalysis concept and its ability to mimic nature's use of water as a reagent in asymmetric conjugate-addition reactions in water.

Methods

Representative procedure: asymmetric hydration of 1a catalysed by DNA–Cu–L1$(NO_3)_2$. A 15 ml aqueous solution of the copper(II)–**L1** complex (0.3 mM) and st-DNA (1.3 mg ml^{-1}) in 2-(*N*-morpholino)ethanesulfonic acid (MES) buffer (20 mM, pH 5.5) was prepared by mixing 10 ml of a st-DNA stock solution (2 mg ml^{-1} st-DNA in 30 mM MES buffer, pH 5.5, prepared 24 hours in advance) with 5 ml of a filtered solution of $Cu(NO_3)_2$ (0.9 mM) and ligand **L1** (1.2 mM) in water. **1a** (2.9 mg) was added to the catalyst solution (15 μmol, final concentration 1 mM) dissolved in 30 μl of CH_3CN. The reaction was mixed by continuous inversion at 5 °C. The crude product was isolated by extraction with Et_2O (2 × 10 ml), drying on Na_2SO_4 and concentration *in vacuo*. The enantiomeric excess was determined by HPLC, using a chiral stationary phase. An analytically pure sample of **2a** was obtained after column chromatography (SiO_2, hexanes:ethyl acetate).

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Author contributions

A.J.B., B.L.F. and G.R. conceived the project; A.J.B., D.C. and G.R. designed the experiments; A.J.B., D.C., D.G. and F.R. performed the experiments and analysed the data. A.J.B., B.L.F. and G.R. co-wrote the paper. All authors discussed the results and commented on the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/. Correspondence and requests for materials should be addressed to B.L.F. and G.R.